Understanding the total airway response to exercise: current perspectives and future challenges

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ABSTRACT

Exercise places a unique set of physiological demands on the airway tract. Historically, most work in this area has focused on the lower airway response, however it is now becoming increasingly apparent that the structural and functional behaviour of the upper airway and large central airways is equally important. Dysfunction in these sections of the airway tract can act to either hinder or modulate the exercise ventilatory response and as such lead to an increased work of breathing and the development of troublesome respiratory symptoms. This article provides an overview of the way in which the entire airway tract is challenged by the heightened ventilatory state mandated by physical activity, highlighting recent developments in our understanding of the physiology of laryngeal, large central and lower airway function during exercise.

INTRODUCTION

Exercise places a unique set of physiological demands on the respiratory system. Even low levels of physical activity mandate an immediate rise in minute ventilation (V_E) and vigorous exertion is recognised to place significant physical, thermal and chemical stress on the structures of the airway tract. Indeed, it has long been recognised that high-intensity exercise, particularly when performed in certain environments (e.g. cold dry air), can promote the development of airway hyper-responsiveness, manifest as exercise-induced bronchoconstriction (EIB) (1, 2).

Over the past decade it has also become increasingly evident that physical exertion also places specific demands on other components of the airway tract, notably the upper airway (i.e. laryngeal region) (3) and large central airways (i.e. trachea and main bronchi (4). As peak airway resistance is typically below the 5^{th} airway generation, the upper sections of the airway tract have historically been most often viewed as a relatively passive 'conduit', acting simply to facilitate the bulk-flow of air for distal gas exchange. It is now apparent however that the structural and functional behaviour of these components of the airway tract can act to either hinder or modulate the exercise ventilatory response and thus result in the development of troublesome respiratory symptoms (5). Accordingly, studies have recently described a high prevalence of excessive laryngeal closure during exercise (6); a condition termed exercise-induced laryngeal obstruction (EILO), that can be viewed as being 'maladaptive', by impairing airflow and increasing the work of breathing (7).

There has also been an improved appreciation of the role of the large or central airway response to exercise. An exaggerated pattern of large central airway collapse, termed excessive dynamic airway collapse (EDAC) appears to be a prevalent co-morbidity in chronic obstructive pulmonary disease (COPD) (6) and severe asthma, yet may also be prevalent in

young, otherwise healthy, athletic individuals with exertional breathlessness (8). This problem is not reliably identified with static physiological measures (9) and yet intervention is important because strategies such as the application of positive pressure ventilation and pursed lip breathing have been shown to enhance exercise capacity in some individuals (10, 11).

This review provides a clinical and physiological overview of the way in which the airway tract responds to exercise. The review is divided by anatomical sections of the airway; namely the upper (i.e. covering laryngeal closure), large airway (i.e. covering tracheal and large central bronchi physiology) and lower (i.e. pertaining to bronchoconstriction) (Figure 1), but with the appreciation that the 'airway response' must be viewed as the integrated outcome of the entire respiratory system.

UPPER AIRWAY RESPONSE

Structure and function

Many of the established physiological models of breathing consider the upper airway and larynx to represent a relatively fixed or static component of the conductive airways. As such, they fail to address the complexity and impact of the dynamic functional properties of the larynx. Although vocalisation and airway protection are considered the main functions of this multi-purpose organ, its valve-type structure represents a considerable flow-limiting point in the airway tract. In healthy individuals, the glottic opening has a smaller cross-sectional area than both the hypopharynx and trachea (Figure 2) (12). Thus, in situations of heightened V_E the larynx effectively becomes an airflow 'choke-point', increasingly exposed to the Venturi effect. As airway resistance is proportional to airway radius to the fourth power (law of Poiseuille) even small decreases in airway diameter may impact significantly on airway

resistance. The larynx normally facilitates airflow by abduction of the vocal folds, in order to increase the cross-sectional area of the glottic inlet (13).

Recent work however has revealed that a significant proportion of young individuals (up to 7% in some series) may be susceptible to inappropriate closure of the larynx during exercise - detected via continuous laryngoscopy during exercise (CLE) (Figure 3) (14, 15). This has led to the identification of several common conditions, collectively termed EILO, whereby closure of the laryngeal inlet impacts breathing during strenuous exertion, whilst appearing and behaving normally at rest (16). In athletes, closure is most often observed at the supraglottic level (i.e. collapse of the arytenoid region) and less frequently at the glottic level (i.e. closure at the level of the vocal folds) (17). It is currently not clear why this condition arises or the underlying pathophysiological mechanisms, but it is likely that an interplay exists between several different mechanisms, including a potential structural inadequacy of laryngeal structures in young individuals (4).

Physiological impact of upper airway / laryngeal dysfunction during exercise

The development of EILO is closely related to exercise intensity; the degree of obstruction typically being maximally evident at peak exercise intensity (18). Individuals with laryngeal obstruction experience breathlessness and audible breathing sounds during the inspiratory phase of the breathing cycle (i.e. stridor).

The increased inspiratory resistance that develops during episodes of laryngeal closure leads to an increase in work of breathing and heightened neural respiratory drive (7); this coincides with breathing pattern changes of increased tidal volumes (V_T) and a slight decrease in breathing frequency, except at peak exercise. In a recent study by Walsted et al. (7) these changes in ventilatory pattern were evident in those with subsequent EILO, compared with matched healthy controls. This breathing pattern appeared to precede any visible laryngeal

obstruction, during an incremental exercise test. This has been confirmed in a recent study in young individuals with EILO and healthy controls, examining ventilatory patterns in EILO using optoelectric plethysmography (19, 20). The study found increased V_E, inspiratory duty cycle and end-expiratory lung volumes, but no difference in V_T. This also correlates with experimental data (i.e. increased oxygen uptake, reduced breathing frequency and enlargement of tidal volume to maintain V_E) from artificially induced fixed airway obstruction when applied to healthy individuals during exercise (21). In the study by Walsted et al. there was no differences in perceived dyspnoea intensity between patients and control subjects, despite increased neural respiratory drive and this may relate to perceptive adaptation in individuals with EILO (7). Whilst speculative, it is hypothesised that the altered ventilatory pattern (i.e. increased V_E and V_T and decreased breathing frequency) might be an adaptive response to maintain ventilation, or a consequence of a maladaptive metabolic response to modulate carbon dioxide clearance particularly during heavy exercise due to the onset of metabolic acidosis. Certainly, further research is required in this area to further delineate the physiological interactions between the larynx, the diaphragm and to better understand dyspnoea.

The consequences of these physiological adaptations on athletic performance have not been systematically studied but several potentially limiting factors may apply including the impact of an increased work of breathing relating to development of dyspnoea and perception of effort in a competitive sporting environment.

LARGE AIRWAY RESPONSE

Structure and function

The 'large' airways are typically defined as the section of the airway tract that extends from the immediate sub-glottis to the end of the large bronchi and includes the trachea, carina and

left and right main bronchi. Recently, there has been increased focus on the role of this section of the airway under physiological stress; e.g. when performing forced expiratory manoeuvres and/or during exercise.

In health, the muscular posterior segment of the trachea closes partially (i.e. up to 50% reduction in tracheal lumen) during expiration, principally to facilitate cough and airway clearance. In some individuals this inward movement may however become more marked and deemed 'excessive'. This phenomenon appears to be most apparent in several clinical 'airway' conditions, such as COPD, or in those in which the inter-pulmonary pressure gradient is altered in favour of airway closure; e.g. obesity.

There is currently a lack of consensus regarding the diagnostic criteria or level of closure that constitutes 'excessive' dynamic airway collapse (EDAC) and whilst a >50% reduction in airway calibre is often taken as 'abnormal', this level of collapse can be observed in normal healthy individuals. Moreover, EDAC is typically diagnosed at either bronchoscopic assessment or during supine computer tomography (CT) imaging, acquired typically during a dynamic 'forced' expiratory respiratory manoeuvre and it is not clear how this relates to more physiologically relevant challenges, such as upright exercise.

Physiological impact of large airway dysfunction during exercise

The physiological impact of dysfunction in this section of the airway is complex and is currently poorly understood. It is apparent from catheter-based studies, evaluating airway flow, that there is a disconnect between what may be observed to be excessive 'collapse' and what is physiologically 'relevant' or causing physiological impact; i.e. what may appear to be excessive collapse may actually not impact flow within the airway tract (22). Indeed, in a cohort of patients with COPD, the degree of central airway collapse was found to be independent of other markers of disease severity, such as lung function, functional capacity and symptom

burden (9). Recently Weinstein and colleagues (23) evaluated military personnel with unexplained exertional breathlessness and wheeze and found EDAC (defined as >75% collapse) as the likely cause of breathlessness in a case series. The response to therapeutic intervention is not clearly described and indeed the optimum therapeutic algorithm for EDAC remains to be fully determined. Recent work however suggests that the application of non-invasive positive pressure ventilation during exercise can increase exercise tolerance (6) and is likely to be favoured initially over other options such as stent placement or tracheal surgery (6).

LOWER AIRWAY RESPONSE

Structure and function

The lower or small airways extend from the main bronchi and are typically defined as those with an internal diameter of less than 2mm that occur at approximately generation eight of the tracheobronchial tree (24). The lower airways differ both structurally and physiologically from large airways; they lack cartilaginous support and mucous glands and there is a surfactant lining which reduces surface tension to prevent closure during expiration and at low lung volumes (25).

The 'normative' or physiologically appropriate airway response to vigorous exercise in both healthy and asthmatic individuals is the development of mild bronchodilation (primarily due to withdrawal of vagal cholinergic tone) (26). However, it is now well established that a significant proportion of otherwise healthy individuals exhibit an 'abnormal' or pathophysiological airway response to intense exercise exposure (27). Indeed, it is estimated that approximately 10% of the general population and up to 70% of elite endurance athletes experience transient lower airway narrowing during and/or post vigorous physical exertion (28).

For individuals performing frequent or repeated bouts of vigorous exercise over a sustained period of time (i.e. endurance athletes) it is thought that dehydration of the small airways and increased forces exerted to the airway epithelium may actually cause lower 'airway injury' (2). Indeed, biomarkers of epithelial damage have recently been reported to correlate directly with achieved ventilation during continuous moderate intensity exercise (29). Furthermore, non-volitional lung function assessment have recently detected evidence of low-grade airway remodelling in athletes with EIB in comparison to healthy counterparts (30).

Although the most appropriate methodology and criteria to secure a diagnosis of EIB remains debated (31-33), it is widely recognised that due to the limited value of a symptom-based approach to diagnosis (34), indirect bronchoprovocation should be conducted to objectively confirm evidence of airway narrowing prior to initiating treatment. In this context, exercise challenge testing or eucapnic voluntary hyperpnoea are most often employed for this purpose (35).

Physiological impact of small airway dysfunction during exercise

Exercise-induced bronchoconstriction is primarily considered a post-exercise phenomenon and thus argued to have limited relevance or impact on exercise capacity or performance. Despite limitations in available methodologies to evaluate in-exercise airflow (i.e. the lower airways are relatively inaccessible), bronchoconstriction has the potential to impede performance through several physiological mechanisms (for a detailed review see Price et al) (36). For example, individuals experiencing bronchoconstriction (particularly athletes achieving high ventilation rates during heavy exercise) are susceptible to an increase in end-expiratory lung volume (EELV) and development of dynamic hyperinflation (37). Alterations to EELV may inhibit or impair the mechanical efficiency of breathing (i.e. increase respiratory muscle oxygen cost) and therefore potentially reduce skeletal muscle blood flow via a

respiratory muscle metaboreflex (i.e. increased sympathetic vasoconstrictor outflow) (38). In addition, it has been proposed that lower airway narrowing may also contribute to ventilation-perfusion abnormalities potentially leading to arterial hypoxemia, reduced gas exchange and/or impaired oxygen uptake dynamics or 'kinetics' (39, 40). Taken together, these factors may contribute to increased work of breathing and/or heightened perception of dyspnoea.

Although it is logical to conclude that bronchoconstriction likely has a deleterious impact on respiratory function and exercise performance, it is important to note that recent findings have indicated pre-exercise airway function (whether bronchodilated or bronchoconstricted) does not impede the ventilatory response to exercise in individuals with variable expiratory airflow limitation (41). Furthermore, the most recent series of performance-based studies evaluating the impact of high-dose short-acting bronchodilator therapy in trained cyclists with EIB failed to detect a meaningful difference in time-trial performance despite observing significant improvements in resting lung function (42, 43) .

SUMMARY AND FUTURE RESEARCH PRIORITIES

Our understanding of the stress placed on the entire airway tract during exercise has evolved significantly over the past decade. As such, sections of the airway that were historically viewed as simple conduits are now recognised to play an important role in modulating airflow with important consequences for ventilatory mechanics, thoracic loading, work of breathing and dyspnoea. Moreover, any pathological condition that affects a section of the airway tract has the capability to have an impact on the more proximal or distal regions (44, 45) and thus overall it would appear somewhat facile to simple consider the impact of laryngeal closure alone without considering downstream effects on small airway function. To this end, Baz et al. (44) Hull et al. (46) previously showed that excessive laryngeal closure during the expiratory phase of respiration may actually modulate lung emptying, in the context of chronic airflow

obstruction. As such, this integrated response could be viewed as an 'adaptive' as opposed to 'maladaptive' state. Future work therefore needs to focus on the development of physiological models of performance to obtain an 'integrated' view of the entire airway tracts response to exercise; with consideration for specific disease endotype(s) and phenotype(s) (Table 1). Additional challenges include the requirement to establish accurate measurements of pressure change and flow across the airway tract during exercise. Recent work highlights the feasibility of this approach when applied to the upper airways (47) but future work should provide an integrative view of changes across the entire airway tract.

In conclusion, the airway tract faces several challenges to respond effectively to the heightened ventilatory state mandated by exercise. This response should be viewed in an integrated way, but to truly understand the physiological response and clinical symptoms that may arise during exercise, requires an appreciation of not only small airway function but the response of the entire airway tract.

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First paper to report that exercise-induced laryngeal closure is associated with increased work of breathing and neural respiratory drive. Also describes changes in ventilatory pattern that appear to precede the develooment of laryngeal closure.

****Olin JT, Clary MS, Fan EM, Johnston KL, State CM, Strand M, et al. Continuous laryngoscopy quantitates laryngeal behaviour in exercise and recovery. The European respiratory journal. 2016;48(4):1192-200.**

Important paper characterising the onset of larygneal obstruction during progressive incremental exercise. Highlighting that larygneal closure develops at higher intensities of exercise; i.e. >80% peak exercise capacity.

***Fretheim-Kelly Z, Halvorsen T, Heimdal JH, Strand E, Vollsaeter M, Clemm H, et al. Feasibility and tolerability of measuring translaryngeal pressure during exercise. The Laryngoscope. 2019.**

Reports feasiility of larygneal flow measurement during exercise. Indicating that this is possible in healthy individuals. This should inform future work to better understand larygneal physiology during exercise.

***Weinstein DJ, Hull JE, Ritchie BL, Hayes JA, Morris MJ. Exercise-associated excessive dynamic airway collapse in military personnel. Annals of the American Thoracic Society. 2016;13(9):1476-82.**

Important clincial report indicating that large airway collapse may be associated with unexplained breathlessness and wheeze in highly trained individuals. Therapeutic interventions now need to be described and explored in further detail.

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Elequoent study in patient cohort with COPD who have apparent excessive expiratory phase larygneal closure. This appears to be associated with lung emptying and may be considered akin to pursed-lip breathing; i.e occuring at the level of the larynx.

TABLE HEADER

Table 1. The total airway response to exercise - what do we need to know?

FIGURE LEGEND(S)

Figure 1. Schematic detailing the anatomical sections of the total airway tract.

Figure 2. Relevant anatomical structures and landmarks in the upper airway: (A) axial plane (laryngoscopic view) and (B) mid-sagittal plane. Note the position of the cuneiforme/corniculate tubercles and the aryepiglottic fold in relation to the vocal folds.

Reproduced with permission from Walsted ES. Evaluating diagnostic approaches in exercise-induced laryngeal obstruction. 2018; (Doctoral thesis).

Figure 3. Continuous laryngoscopy during exercise. The laryngoscope is placed in situ and secured to a headset via a facemask. The screen(s) provide real-time feedback of the structural and functional behaviour of the larynx and gas exchange during cycling.

Table 1.

Airway tract	Physiological response to exercise	Pathophysiological response to exercise	Impact of airway dysfunction	Future research: what do we need to know?
Larynx / upper airway	• Abduction of the vocal folds facilitates airflow by increasing the cross-sectional area of the glottic opening	• Exercise-induced laryngeal obstruction (EILO) • Glottic closure - i.e. adduction of the vocal folds • Supraglottic closure - i.e. collapse of the arytenoid region	• Increased work of breathing and neural respiratory drive • Increased tidal volume and decreased breathing frequency below maximal exercise • Altered ventilatory pattern / breathing mechanics	• Further knowledge and understanding of laryngeal physiology during exercise • Determine the physiological interactions between the larynx and the diaphragm • Improve understanding of EILO and perceived dyspnoea • Determine the impact on exercise capacity utilising relevant 'performance' based trials (e.g. critical power methodology)
Large central airways	• Posterior segment of trachea closes partially during inspiration; i.e. >50% tracheal lumen diameter	• Exercise dynamic airway collapse (EDAC) • Posterior segment of trachea closes 'excessively' during inspiration - i.e. >75% tracheal lumen diameter	• Development of expiratory wheeze and loud barking / honking type cough • Difficulty with airway clearance leading to recurrent infection • Altered breathing mechanics and flow volume lop alterations	• Understand how the large airways behave during physiologically relevant challenge - i.e. walking • Develop diagnostic tests that can provide insight regarding the impact of airway collapse during a physiologically relevant challenge • Develop simple potentially bio-absorbable scaffolding mechanisms to improve tracheal patency
Lower / small airways	• Vagal cholinergic tone withdrawn resulting in mild bronchodilation to facilitate airflow and optimise gas exchange	• Exercise-induced bronchoconstriction (EIB) • Transient airway narrowing - i.e. 10-15% pre-to post; exercise reduction in FEV_1	• Increased work of breathing and/or heightened perception of dyspnoea • Increased end-expiratory lung volume and development of dynamic hyperinflation • Impaired ventilatory mechanics • Increased respiratory muscle oxygen cost • Ventilation-perfusion mismatch • Impaired oxygen kinetics	• Establish widespread consensus concerning diagnostic test criteria • Define specific EIB phenotypes/endotypes • Evaluate susceptibility to respiratory tract infection • Determine the impact on exercise capacity utilising relevant 'performance' based trials (e.g. critical power methodology) • Consideration for gender, disease sub-type, severity, sporting discipline and athletic standard remains a priority

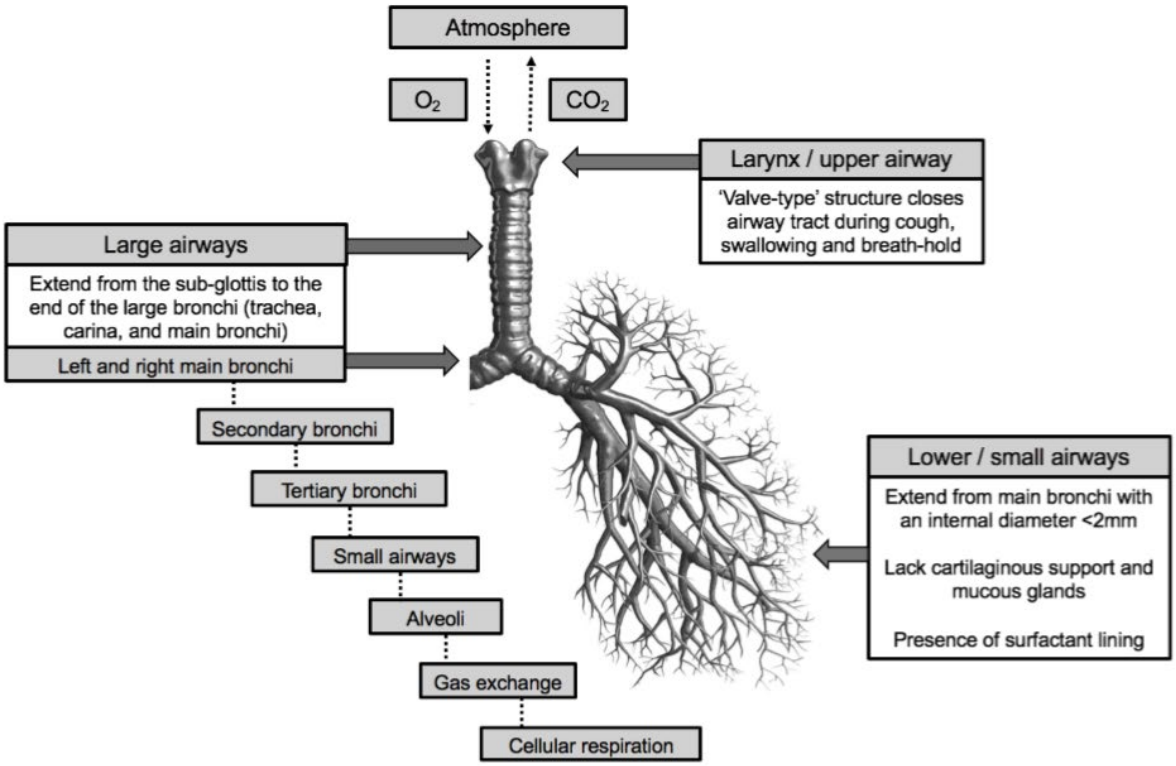
Atmosphere
O_2
CO_2
Larynx / upper airway
'Valve-type' structure closes airway tract during cough, swallowing and breath-hold
Large airways
Extend from the sub-glottis to the end of the large bronchi (trachea, carina, and main bronchi)
Left and right main bronchi
Secondary bronchi
Tertiary bronchi
Small airways
Alveoli
Gas exchange
Cellular respiration
Lower / small airways
Extend from main bronchi with an internal diameter <2mm
Lack cartilaginous support and mucous glands
Presence of surfactant lining

Figure 1.

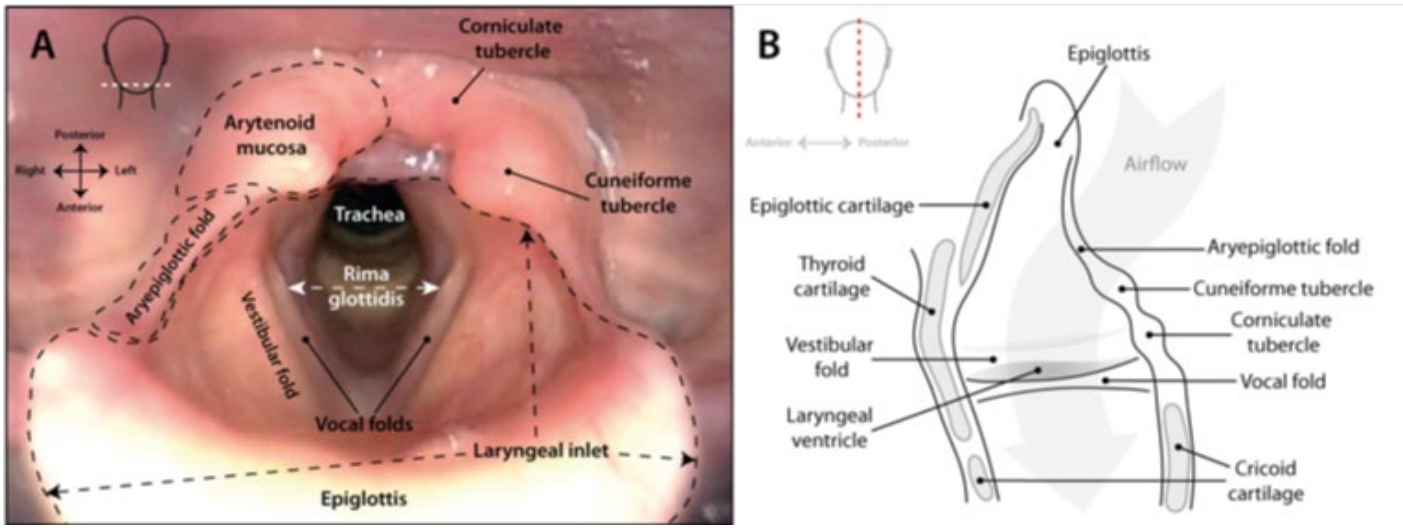
A
Corniculate tubercle
Arytenoid mucosa
Posterior
Right
Left
Anterior
Cuneiforme tubercle
Trachea
Aryepiglottic fold
Rima glottidis
Vestibular fold
Vocal folds
Laryngeal inlet
Epiglottis
B
Epiglottis
Airflow
Epiglottic cartilage
Aryepiglottic fold
Thyroid cartilage
Cuneiforme tubercle
Corniculate tubercle
Vestibular fold
Vocal fold
Laryngeal ventricle
Cricoid cartilage

Figure 2.

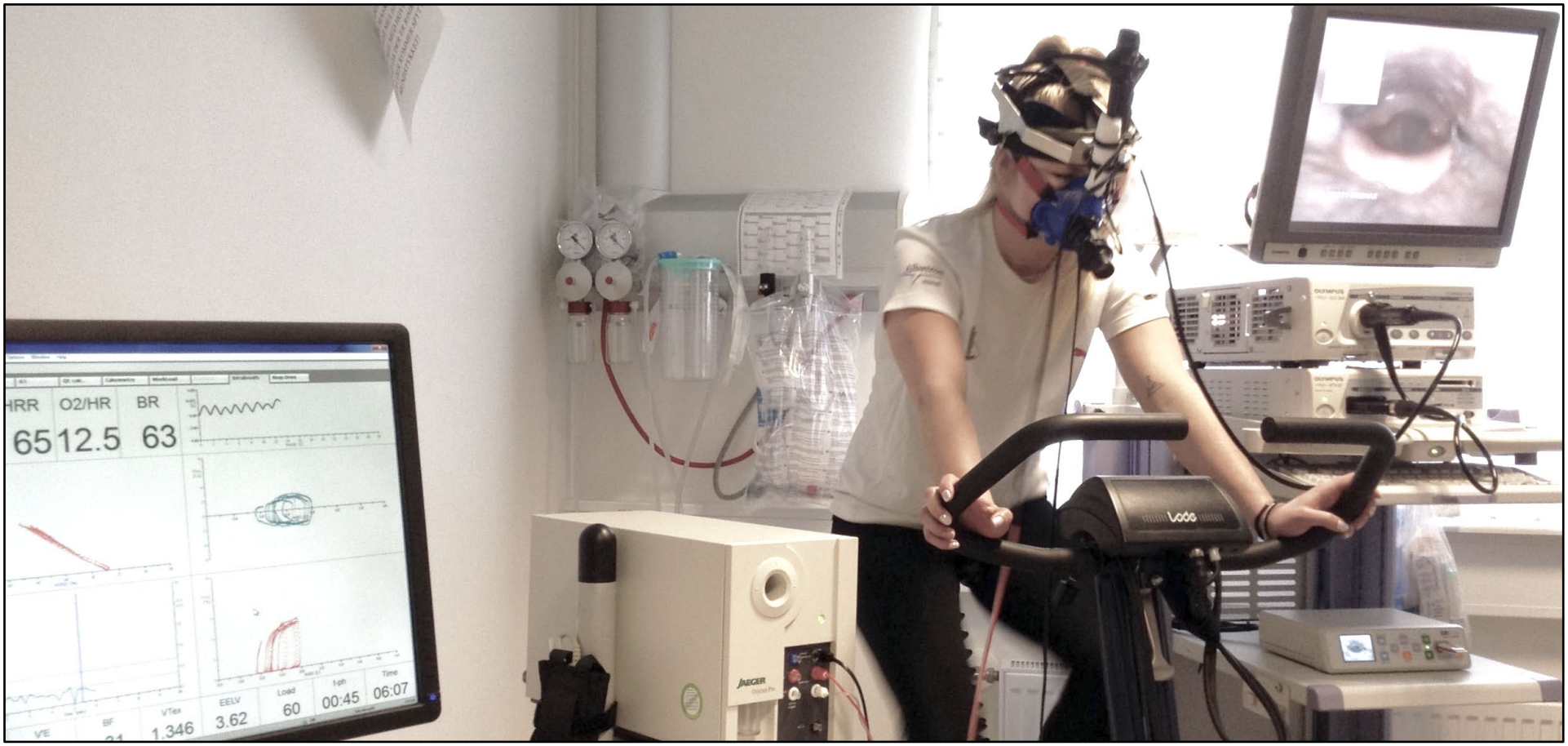
HRR O2/HR BR
65 12.5 63
VTex EELV Load t-ph Time
1.346 3.62 60 00:45 06:07
JAEGER
Lode

Figure 3.